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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,845	05/16/2006	Filippo Giancotti	MSK.P-076	7804

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Marina Larson & Associates LLC
re: MSK
P. O. BOX 4928
DILLON, CO 80435-4928

EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
10/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,845	GIANCOTTI, FILIPPO	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-10 and 15-20* is/are pending in the application.

4a) Of the above claim(s) *6,10,16,18 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,7-9,15,17 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/5/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 8/5/08, is acknowledged.

2. Claims 1-3, 5-10 and 15-20 are pending.

3. Claims 6, 10, 16, 18 and 20 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 1-3, 5, 7-9, 15, 17 and 19 are under consideration in the instant application as they read on a method for inhibition of angiogenesis in a tissue expressing α6β4 integrin, comprising the steps of exposing the tissue to a therapeutic agent effective to reduce the amount of active α6β4 integrin in the tissue, wherein the therapeutic agent targets β4, wherein the therapeutic agent is an antibody.

5. Applicant's IDS, filed 8/05/08, is acknowledged.

6. In view of the amendment filed on 8/5/08, only the following rejections are remained.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-3, 5, 7-9, 15, 17 and 19 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons set forth in the previous Office Action mailed 4/07/08.

Applicant's arguments, filed 8/05/08, have been fully considered, but have not been found convincing.

Applicant contested the use of Kennel reference and Sepp reference on the basis that the Examiner never offers any explanation of how the selected teachings contribute to the argument of non-enablement. Applicants submit that they are unable to respond to the rejection to the extent it is based on these references.

However, applicant claims that a therapeutic agent that effective to reduce the amount of active α6β4 integrin in tissue, wherein the therapeutic agent targets and inhibits the signaling function of β4, thereby inhibiting pathological angiogenesis. Sepp et al reference teach stimulation of microvascular endothelial cells (by definition angiogenesis) with basic fibroblast growth factor or phorbol 12-myristate 13-acetate, agents previously shown to induce endothelial cell migration

in vitro, resulted in a marked decrease in cell-surface expression of the β4 mRNA (see abstract and page 267-268 4th and 5th full ¶). In simple terms, agents that reduce the amount of active α6β4 integrin in tissue, target and inhibit function of β4 such as PMA and bFGF would promote angiogenesis not inhibiting pathological angiogenesis as claimed. In other words, the claimed agents would mimics the normal effects of angiogenic factors *in vivo* rather than the anti-angiogenic effect as claimed. Therefore, the claimed method is not enabled.

Applicant just points to the teachings of Nguyen article shows results concerning the role of β4 expression with respect to angiogenesis and suggests that is may cause arrest of angiogenesis.

However, Applicant does not dispute the facts presented in Nguyen articles. Further Applicant ignores Hiran's et al teachings that α6β4 is not expressed during developmental angiogenesis.

Applicant points to the Lipscomb reference barely mentions angiogenesis, but rather presents results relating to the role of integrins in tumorigenesis. When it does discuss angiogenesis, Lipscomb cites to the publication based on the work disclosed in the present application and the evidence of non-universality which the examiner relies on as part of his argument is in fact disclosed in the present application. (Page 23). Neither the disclosure in the application of a limited number of negative test results, nor the subsequent publication of these results is a basis for an enablement rejection. (See MPEP § 2164.08(b)) Thus, Applicants submit that the alleged basis for finding a lack of enablement is incomplete and inaccurate, and that the rejection should therefore be withdrawn.

However, while applicant's specification discloses that the role of α6β4 in tumor angiogenesis may not be universal, yet, applicant is claiming inhibiting any pathological angiogenesis in a tissue prone to pathological angiogenesis and expressing α6β4 integrin. It would appear that using β4 signaling inhibiting agents in the claimed methods is unpredictable. Thus faced with contradictory and seemingly mutually exclusive results regarding the activity of the signaling function of β4 molecule, undue experimentation would be required of the skilled artisan to determine the effect of the therapeutic agents which reduce the amount of active α6β4 integrin in the tissue, targets and inhibits the signaling function of β4 on any particular angiogenesis response in vivo in view of the instant disclosure and the unpredictability of the art on the effect of the β4 molecule on angiogenesis.

Applicant agrees with the conclusion that prior to the present invention there was a lack of knowledge as to the actual role of β4 with respect to angiogenesis. In making the enablement rejection in this case, however, the Examiner is improperly considering just the extrinsic references, and fails to include the specific results in the specification in the assessment of whether the application considering all of the evidence provides a credible enabling disclosure. In the absence of expressly described consideration of the entire body of evidence including the results in the specification, Applicants submit that the Examiner has failed to meet the burden to present a prima facie case for lack of enablement to which Applicants are required to respond. Nevertheless, Applicants point out that the specification provides many additional experimental

results, all of which support the conclusion that inhibition of the signaling functions of β4 leads to a reduction in angiogenesis.

The mice which are used in the experiments described in the present invention are not deficient in β4 as a whole but rather have a deletion in C-terminal signaling portion of the protein. (Page 15, lines 20-21). Thus, the β4 in these mice retain the adhesion functions of β4, and the experiments with the mice isolate one of the two functions of β4 for study. These two functions, adhesion and signaling, are suggested to be temporally and functionally distinct. (See Lipscomb, Page 10970, Col. 2).

Using the mouse model, it was shown in the test results in the application that there were no macroscopic defects in the mice, indicating that β4 signaling was not required during embryonic vasculogenesis and angiogenesis. (See Page 17) This difference can in part account for the differing results in the studies relied on by the Examiner. The specification further reports that substantial amounts of α6β4 was detected in medium and large vessels of five diverse types of tumors: papillary thyroid carcinoma, prostate cancer, breast cancer and glioblastoma multiforme (See Page 17) and melanoma (Page 18). Angiogenesis in four tumor types (melanoma, Lewis lung carcinoma, lymphoma and fibrosarcoma) was shown to be reduced in mutant mice as opposed to wild type mice. (Page 23). Thus, the specification provides real evidence of the important relationship between β4 signaling and pathological angiogenesis, and this evidence is not contradicted by the cited references. As such, Applicants submit that the present application provides a fully enabling and credible disclosure and that the rejection should be withdrawn.

However, the specification fails to show the same effect with an agent that effective to reduce the amount of active α6β4 integrin in the tissue, targets and inhibits the signaling function of β4. The art of Sepp et al teach that PMA and bFGF agents which decrease in cell-surface expression of the β4 integrin chain, associated with a decrease in β4 mRNA, induce endothelial cell migration. Sepp et al teachings contradict the claimed method. The influence of a scientific theory should depend on its empirical and demonstrable aspects and not its underlying logic. Yet, such empirical and demonstrable aspects of the claimed method for inhibition of pathological angiogenesis in a tissue with therapeutic agents such as anti-β4 antibody are lacked in the instant specification. No working empirical data demonstrating that the anti-β4 antibody would inhibit pathological angiogenesis is disclosed.

9. Claims 1-3, 5, 7-9, 15, 17 and 19 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 4/07/08.

Applicant's arguments, filed 8/05/08, have been fully considered, but have not been found convincing.

Applicant argues that the term "tissue expressing α6β4 integrin" the common structural feature that is recognized in the specification and in the term itself is the structural feature of expressing α6β4 integrin. Furthermore, as to the breadth of this term and "pathological angiogenesis in a tissue expressing α6β4 integrin" the Examiner's attention is directed to the disclosure on Pages 7-8, and to the multiple tumor types tested in the experiments in the application. The assertion on Page 5 of the Office Action that a person skilled in the art is supposed to go figure out for themselves what a relevant tissue or a pathological angiogenesis in a relevant tissue looks like is specious, and assumes that the person skilled in the art has no skills at all. This is plainly in error on two counts.

However, the examiner directs applicant's attention to Hiran et al teachings that α6β4 is not expressed during developmental angiogenesis. While the specification on pages 7-8 list several species of pathological angiogenesis diseases, however, none of these species has been show to express α6β4 integrin during angiogenesis.

Applicant submits that the Examiner states that "the specification fails to provide anti-β4 or RNAi that blocks activate signal transduction that can be used in the claim method." Leaving aside the fact that this sentence is not clear and appears to be inherently contradictory, Applicants direct the Examiner's attention to the disclosure of two antibodies to β4 on Pages 12-13 of the application, a specific β4 targeting oligonucleotide therapeutic agent (Seq. ID No. 4 on Page 12), and a human integrin β4 binding protein (Seq. ID No. 1, Page 10). Furthermore, since the nature of the deletion in the C-terminal region of 134 identifies the region responsible for signaling, isolation and identification of additional therapeutic agents is within the skill in the art using ordinary and conventional techniques and techniques such as those described in the section entitled Screening Assays beginning on Page 13. Thus, Applicants submit that the rejection for lack of written description is in error and should be withdrawn.

It is the examiner's position that the prior of Sepp et al teachings that inhibiting the signaling function of β4 does not lead to the inhibition of angiogenesis. Accordingly, it is not clear that the listed human and mouse RNAi species and anti-β4 antibodies would function as claimed. With respect to the two anti-β4 antibodies disclosed in the specification, they have not been show to inhibit β4 integrin signaling. Applicant fails to address the issue with respect to the "agent targets and inhibits the signaling function of β4" , the rejection is maintained for reasons of record.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e1) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another

filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

35 U.S.C. § 102(e), as revised by the AIPA and H.R. 2215, applies to all qualifying references, except when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. For such patents, the prior art date is determined under 35 U.S.C. § 102(e) as it existed prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. § 102(e)).

11. Claims 1-3, 5, 7-9, 15, 17 and 19 stand rejected under 35 U.S.C. 102(e)/(b) as being anticipated by US 20030224993 (IDS reference)/WO 02/30465 for the same reasons set forth in the previous Office Action mailed 4/07/08.

Applicant's arguments, filed 8/05/08, have been fully considered, but have not been found convincing.

Applicants submit that the Examiner has inappropriately combined and confused legal standards relating to composition or article claims, by trying to apply them to method claims. It is certainly true that under US law, discovery of a new use for an old composition will not make that composition patentable again, even if the statement of intended use is included in the claims. The same is not the law with respect to method claims. In the case of a method claim, a showing of anticipation requires that practicing the method described in the art would inherently (i.e. necessarily) achieve the undisclosed result which it the object of the claimed method, i.e. inhibiting angiogenesis. Exparte Levy, 17 USPQ2d 1461, 1464 (BPAI 1990)(To establish anticipation under the theory of inherency, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.") The Examiner cannot meet this requirement by ignoring it. Further, the prior disclosure must be one that places the public in possession of the invention as claimed, i.e. in possession of the knowledge that elimination/reduction of the [34 signaling will result in reduced angiogenesis. In re Marshall, 198 USPQ 344, 346 (CCPA 1978)(If anyone ever lost weight by following the PDR teachings it was an unrecognized accident. An accident or unwitting anticipation of an invention cannot constitute an anticipation.").

However, it is noted that the CAFC recently held in Bristol-Myers Squibb Co. v. Ben Venue Laboratories Inc., 58 USPQ2d 1508 (CA FC 2001) that when a claimed process is not directed to a new use, *consists of the same steps described in a prior art reference*, and the newly discovered results of the known process *directed to the same purpose* are inherent, the process is not patentable.

Applicant further pointed out that no experiments described in the '993 publication appear to be of a type that would lead to discovery of information about angiogenesis. The examples are carried out in tissue cultures. Moreover, since β4 integrin is modified through the introduction of a dominant-negative protein and not by antisense reduction in the amount of β4 it is not directly reflective of what occurs when endogenous β4 is reduced, and the observed effects could be due to any of a variety of mechanisms.

However, it is noted that Applicant's specification does not disclose experiments describing administering agents as claimed. Further, a reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed in invention." In re Donohue, 766 F.2d 531,226 USPQ 619 (Fed. Cir. 1985). See MPEP 2121.01. Further, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Regarding the mechanisms of action, the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Even though applicant has proposed the mechanism by which the β4 signaling inhibits angiogenesis does not appear to distinguish the prior art teaching the same methods to achieve the same end-result. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Applicant further submits that claims 1 and 7 now require targeting of the signaling function of β4. Nothing in the cited reference discloses this element of the claims.

It is the examiner's position that the prior art agents such as antisense molecules to beta4 mRNA and antibodies to beta4 integrin would target and inhibit the signaling function of β4 in the absence of evidence to the contrary.

11. Claims 1-3, 5, 7-9, 15, 17 and 19 stand rejected under 35 U.S.C. 102(e) as being anticipated by US 20060172957 for the same reasons set forth in the previous Office Action mailed 4/07/08.

Applicant's arguments, filed 8/05/08, have been fully considered, but have not been found convincing.

Applicant submits that this references makes no mention of angiogenesis, and the Examiner has applied the same erroneous logic. Furthermore, Applicants point out that this reference relates to oligonucleotide inhibitors and that there is no disclosure of using an antibody as a therapeutic agent. Accordingly, the rejection of claims 5, 9, 17 and 19 as anticipated is clearly in error.

The Examiner's position is the same as above. Further the reference teaches an antibody as a therapeutic agent (see ¶9).

12. No claim is allowed.

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

October 14, 2008

/Maher M. Haddad/
Maher Haddad, Ph.D.
Primary Examiner
Technology Center 1600